AMENDMENTS

In the specification

Please replace the paragraph beginning on page 2, line 10, with the following amended paragraph:

As a central player in translation initiation, eIF-4G is a logical target for regulation of cellular protein expression. Mammalian 4E-BP1, 4E-BP2, 43-BP3 (reviewed in Sonenberg, 1996) and yeast p20 (Altmann et al., 1997) inhibit cap-dependent protein synthesis by competing with eIF-4G for binding to eIF-4E. Biochemical studies have demonstrated that eIF-4G and the 4E-BPs occupy mutually-exclusive binding sites on the surface of eIF-4E (Haghighat et al., 1995), thereby blocking assembly of the translation machinery without affecting cap recognition. Sequence analyses of the 4E-BPs and the eIF-4Gs suggest that these two protein families have converges on the same eIF-4E binding strategy, which employs a *Tyr-X-X-X-X-Leu-*ϕ (SEQ ID NO. 21) eIF4E-recognition motif (where X is variable and ϕ is a hydrophobic amino acid, and more particularly Leu, Met, or Phe) (Mader et al., 1995; Altmann et al., 1997). Treatment of cells with mitogens or growth factors upregulates cap-dependent translation, at least in part, by relieving the repressive effects of the 4E-BPs. After phosphorylation of one or more serine and/or threonine residues by the phosphatidylinositol 3-kinase signal transduction pathway, the 4E-BPs are no longer able bind to eIF-4E allowing translation initiation to proceed (reviewed in Sonenberg and Gingras, 1998).

Please replace the paragraph beginning on page 2, line 26, with the following amended paragraph:

"The structures of mammalian (Marcotrigiano et al., 1997) and yeast (Matsuo et al., 1997) eIF-4E bound to the cap analog 7-methyl-GDP resemble a cupped hand, consisting of a curved, 8-stranded antiparallel β-sheet, backed by three long α-helices. The cap analog binds in a narrow slot on the molecule's concave surface. 7-methyl-guanine recognition by eIF-4E is mediated by π–π stacking between two conserved tryptophans and three Watson-Crick-like hydrogen bonds, involving a backbone amino group and the side chain of a conserved glutamate. The methyl group

makes a van derWaals contact with a third conserved tryptophan. On its convex dorsal surface, eIF-4E displays a phylogenetically-invariant hydrophobic/acidic portion (see Fig. 5B in Marcotrigiano et al., 1997) that was predicted to be the binding site for the *Tyr-X-X-X-X-Leu-ϕ* (SEQ ID NO: 21) motifs of both eIF-4G and the 4E-BPs. This assertion has been partially confirmed by the results of NMR experiments using yeast eIF-4E and mammalian 4E-BP1 (Fletcher et al., 1998).

Please replace the paragraph beginning on page 3, line 5, with the following amended paragraph:

More recently, two high-resolution crystal structures of binary complexes of eIF-4E plus 7-methyl-GDP interacting with eIF-4E-recognition motifs from mammalian eIF-4GII (referred to as the active complex) and 4E-BP1 (referred to as the inhibited complex) were described (Marcotrigiano et al., 1999, Molecular Cell 3:707-716). Therein, it was shown that both oligopeptides bind the same conserved portion of eIF-4E's convex dorsal surface, far from the cap-binding slot. The two *Tyr-X-X-X-X-Leu-ϕ* (SEQ ID NO: 21) motifs adopt identical L-shaped, extended chain/α-helical conformations, stabilized by similar contacts within each peptide and with eIF-4E. Biochemical studies of full-length 4E-BP1 and the two oligopeptides document that they bind eIF-4E with similar affinities, lace secondary structure in the absence of eIF-4E, and inhibit translation in vitro. It was suggested that 4E-BP1 is a molecular mimic of eIF-4G, that undergoes the same disorder-to-order transition on binding to eIF-4E. The resulting competition permits regulation of translation initiation in eukaryotes, which can be overcome by phosphorylation of the 4E-BPs (Marcotrigiano et al., 1999, supra).

Please replace the paragraph beginning on page 32, line 8, with the following amended paragraph:

Figure 7 shows the alignment of 4E-binding sites comprised in a number of diverse eIF4E-binding proteins. The light gray indicates positions at which a mutation to alanine abrogates the binding to eIF4E (Mader et al., 1995; and Poulin et al., 1998). +/- indicate charged amino acids. Φ refers to hydrophobic amino acids. Y and L refer to the standard one letter code for amino acids,

and "." shows that the 4E binding site at this particular position is not dependent on a particular amino acid.